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NEED FOR HARMONIZATION OF LABELING OF MEDICAL DEVICES: A REVIEW

Rajendra K. Songara*[1], Ganesh N. Sharma[1], Vipul K. Gupta[2], Promila Gupta[3]

1. School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan (India)
2. Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak, Haryana (India)
3. Department of Pharmaceutical Sciences, Guru Jambheshwar University, Hisar, Haryana (India)

Corresponding Author's E-mail: - rajendra_songara25@yahoo.co.in

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ABSTRACT

Medical device labeling is any information associated with a device targeted to the patient or lay caregiver. It is intended to help assure that the device is used safely and effectively. Medical device labeling is supplied in many formats, for example, as patient brochures, patient leaflets, user manuals, and videotapes. The European commission has discussed a series of agreements with third countries, Australia, New Zealand, USA, Canada, Japan and Eastern European countries wishing to join the EU, concerning the mutual acceptance of inspection bodies, proof of conformity in connection with medical devices. Device labeling is exceedingly difficult for manufacturers for many reasons like regulations from government bodies to ensure compliance, increased competent authority surveillance, increased audits and language requirements.

Key words: Labeling, Medical device, Regulatory authority.

INTRODUCTION

Medical devices are any instrument, apparatus, implement, machine, appliance, implant, in vitro regent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of: [1, 2, 3].

Diagnostic, prevention, monitoring, treatment or alleviation of disease

Diagnostic, monitoring, treatment, alleviation of or compensation for an injury

Investigation,replacement, modification, or support of the anatomy or of a physiological process
Supporting or sustaining life
Control of conception
Disinfecting of medical devices
Providing information for medical purposes by means of in vitro examination of specimens derived from the human body and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Medical device labeling assists patients or their lay caregivers in understanding the device; its operation, care, and maintenance; the way it interacts with the body to accomplish its purpose; its place and purpose in the patient care regimen; and any safety or disposal issues. Medical device labeling is essential to assure safe and effective use of many, but not all, devices. It informs patients or their lay caregivers about proper use, risks, and benefits of the device in language they can understand [4]. Adequate directions for operating the devices are needed to make devices safe and effective. For example, as more patients use complex medical devices at home, medical device patient labeling becomes necessary to better communicate to the lay person how to operate the device [5].

Devices that might have labeling that would include instructions for use would be those the patient or lay caregiver have to set up, operate, clean, etc. They might include such devices as suction equipment, intravenous infusion pumps, physical therapy equipment, or transdermal electrical nerve stimulation (TENS) devices [6]. Devices that would have labeling consisting primarily or completely of risk/benefit information might be implants that have no external patient interface, once they are implanted, or prescription, diagnostic or therapeutic devices that the patient is actively involved in choosing (e.g., laser eye surgery, lithotripsy, intraocular lenses) [7].

Foreign establishments engaged in the manufacture, preparation, propagation, compounding, or processing of a device that is imported, or offered for import, into the U.S., must register their establishments and provide the FDA with the name of the U.S. agent representing their establishment [8].

Foreign establishments must also continue to file device listing forms for medical devices, they are exporting to the U.S. FDA is also authorized to enter into cooperative agreements with foreign countries to ensure that non-compliant products are refused entry into the U.S. [9].

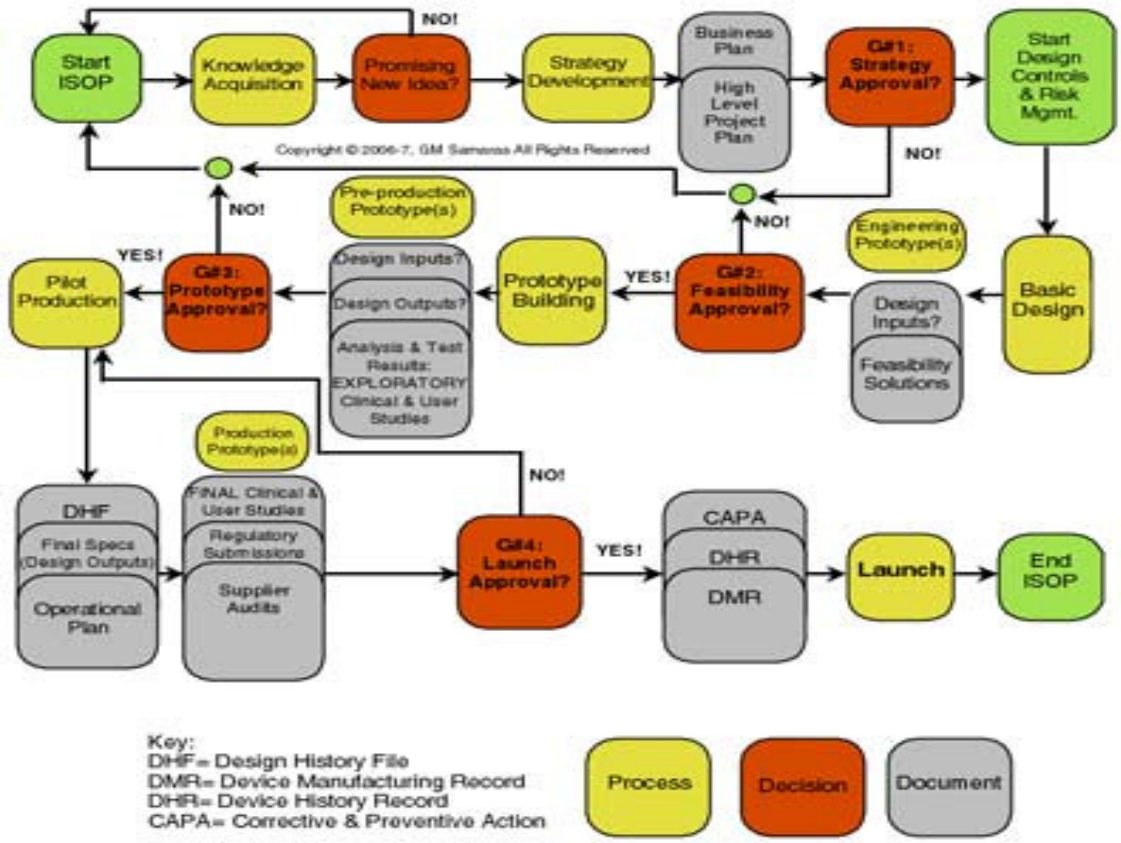


Fig. 1: Innovation standard operating procedure (ISOP) for regulated medical device development under Design Controls

Device labeling is a difficult issue for manufacturers, and the prime cause of this is the insistence on national language by individual countries. For devices and diagnostics that are to be sold across the EU and non-EU European Union countries, poses practical and legal difficulties [10]. The driver for full, comprehensive and local-language labeling is the possibility of litigation if something goes wrong. Yet, there is limited space on labels and, the more information that is included, the less the user is likely to read or, more importantly, absorb the information [9]. Translations may apparently be technically accurate, but are literal and not sensible or idiomatic - the example was given later of 'reverse-pipetting' being translated into German as 'use the pipette upside down' [11]. It would make sense for this to be English - it is the language of international conferences and of medical professionals in general. The fact that professional qualifications are intended

to be portable throughout the EU also makes it a real possibility that a non-national professional would have problems with a national language label and instruction for use even if they speak the language well enough to deal with patients [12].

Some In vitro diagnostic (IVD) companies are considering using separate U.S. and non-U.S. labels. The U.S. labels would contain no symbols, and the non-U.S. labels for the rest of the world would contain symbols [13]. Labeling as a critical component of the device and provides comprehensive requirements for marking and labeling. The standard requires all information for safe installation, use, storage, servicing, and maintenance of the device to be provided to the user. For safety-significant items and for effective use of the device, the standard requires that markings be placed directly on the device [1].

The labeling requirements apply to all medical devices offered for sale in Canada or imported for sale or use in Canada. These labeling requirements do not apply to custom-made, special access devices, nor investigational testing devices [14].

Justification for the need of medical device labeling

Risk / benefit information's are information's, people need to decide to use a device or have it used on them. This information also allows the users to become aware of potential problems with the device [15, 16].

Risks and benefits to the patient or environment associated with the uses of the device

Information about maintaining the device or identifying potential problems with the device

Sufficient descriptive information to tell what the device is and what it is used for

Types of people and situations for whom the device would not be a good choice

Information about maintaining the device or identifying potential problems with the device

Alternative therapeutic and diagnostic choices available

Classification of Medical Devices [17, 18, 19]

The U.S. Congress classifies medical devices in three regulatory classes, according to the level of control deemed necessary to ensure that they are safe and effective. To make the appropriate recommendation to the Commissioner regarding the classification of regulatory control appropriate to a medical device, a classification panel reviews the device

taking into consideration, among other pertinent factors.

This term defines a wide spectrum of products, ranging from tongue depressors to highly sophisticated implantable devices. According to Section 201 of the Federal Food, Drug, and Cosmetic Act (FD& CA), a medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article including any component, part or accessory which is

Class I Medical Devices:

Examples of these are manual stethoscopes, surgical scalpels and forceps. These devices present the least safety risk to the operator or the patient. Thus, they are subject only to the general controls authorized by Section 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification or other remedies), 519 (record and reports), and 520 (general provisions) of the FDA.

Class II Medical Devices:

Examples of these are endoscopes which provide access, illumination, and observation or manipulation of body cavities, hollow organs, and canals; and surgical lasers for many indications. In addition to the requirements of Class I, these devices are subject to performance standards promulgated under Section 514 (performance standards) of the FD&CA. These are devices for which general controls alone are considered sufficient to establish their safety and effectiveness. Special controls include performance standards, postmarket surveillance, patient registries, guidelines and recommendations.

Class III Medical Devices:

These are devices for which, premarket approval is or will be required. They include devices that are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of injury. Examples are indwelling gas analyzers, implantable cardiac pacemakers, cardiac arrhythmia alarms, and automatic heparin analyzers. A device is considered class III if there is not enough information to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness.

Global Harmonization Task Force progress on Harmonization of Labelling Requirements

To harmonize national provisions regarding the safety, health protection, and performance characteristics of medical devices, including the relevant certification and inspection procedures

[20, 35]. The different national systems had created barriers to unrestricted movement of medical devices within the EU marketplace. These requirements relate mainly to the design and construction of devices; their chemical, physical, and biological properties; construction and environmental properties; protection against radiation; and information supplied by the manufacturer, including labeling. Companies may ensure compliance with the essential requirements a number of ways, such as a full quality assurance system, product quality assurance, or a declaration of conformity, depending on the device's characteristics. The company may then affix the CE mark to its device, certifying that the device complies with the essential requirements and is thus entitled to move freely throughout the EU [21].

The Global Harmonization Task Force (GHTF) is a voluntary group of representatives from national regulatory authorities and industry. The purpose of GHTF is to encourage convergence in regulatory practices relating to ensuring the safety, effectiveness/performance and quality of medical devices [22].

Labeling Requirements in Japan

The Japanese market for medical products is estimated to be worth more than $20 billion annually. Medical devices are regulated under Japan's Pharmaceutical Affairs Law administered by the Ministry of Health, Labor, and Welfare (MHLW) [23]. To market a medical product in Japan, a manufacturer must obtain shonin (manufacturing product approval) for high-risk devices ensuring the safety and effectiveness of the product. In addition, a manufacturer needs a kyoka (license). The license provides authorization for an OEM to market products in Japan [13, 24] The Pharmaceutical Affairs Law (PAL) includes changes to medical device labeling requirements, such as appointing a Marketing Authorization Holder (MAH). There are also new GMP requirements and changes in the classification and labeling of medical devices. New information, including the device classification, must be listed on the product insert of all medical devices. The address of the MAH also needs to be included. Prior to the implementation of PAL, the contact information listed on the packaging could be the company's headquarters; now the contact information must be the location where the product's marketing is handled. All devices manufactured overseas should provide the location of the manufacturing site as well. Medical equipment falls into one of three categories depending on the degree of potential risk-highly controlled (high-risk), controlled (low-risk), and general (very low risk).

Labeling Requirements in China

The State Food and Drug Administration (SFDA) in china regulates imported medical devices. The state administration for entry and exit Inspection and quarantine, issues safety licenses for x-ray equipment, dialysis equipment, blood purification equipment, electrocardiographs, implantable pacemakers, and ultrasound equipment. For certain high-risk devices, the China Compulsory Certification (CCC) mark is required. Devices undergo a registration process based on classification. Class III devices, for example, require testing by a Chinese laboratory. All safety information must be in Chinese for high-risk devices [25]. Medical devices imported into china must be labeled in chinese, and include the registration certificate number, product features, and the scope of usage for the product.

These labels should be affixed to products before going through customs. The regulation also required that the consumers should be informed of the related symptom, things to be aware of, and other needed warnings. On perishible products, language or marks noting "perishible use" should be attached, and validity dates should be marked products that need to be used within certain period. This regulation has a number of prohibitions again absolute expressions on efficacy. These include "best effect of treatment", "Full recovery guarantee", "Immediate effect", "Without toxicity and side-effect". Other prohibitions include language providing guarantees such as "Money back if not effective", "highest technology", "most scientific", "most advanced" and "the best"

In addition, the specifications, labels and marks of medial devices can not state cure rate or efficacy rates, comparisons to the efficacy and safety of one manufacturer's products with another's. Making use of the name or image of any firm's or individual's for the purpose of approval or recommendation is not allowed, nor can devices have labels contain such expressions which make people feel that they have attracted certain disease, or which mislead people into feeling that they would contract a certain disease, or their disease could get worse by not using this medical device. U.S. manufacturers are advised to work with their Chinese distributors regarding labeling issues [26].

Labeling Requirements in Brazil

The Brazilian customer protection code requires that product labeling provide the consumer with correct, clear, precise, and easily readable information about the product's quality, quantity, composition, price, guarantee, shelf life, origin, and risks to the consumer's health and safety. Imported products should bear a Portuguese translation of

this information. Since metric units are the official measuring system, products should be labeled in metric units or show a metric equivalent. The labeling requirement for genetically modified organism (GMO) must follow the same procedures as mentioned above, although, GMO is currently being debated in Brazil [27].

Labeling Requirements in Europe

All medical devices must bear a label identifying the name and address of the manufacturer. For devices imported into the community, the label, outer packaging, or instructions for use must also contain the name and address of either the importer or the manufacturer's authorized representative established within the community [28]. The label must contain several additional details, including information to enable the user to identify the device or other contents, as well as any operating instructions, warnings, or precautions to take. If the device's purpose is not obvious to the user, it must be clearly stated on both the label and in the instructions. As a general principle, each device must be accompanied by as much information as is necessary for people to use it safely, taking into account the training and knowledge of the potential users. Certain basic instructions must appear on the label with more detailed copy to be included in the enclosed instructions [29]. The instructions must contain several particulars, including the details required on the label, any side effects from use of the device, and, as a general rule, details for its correct use, including any specific precautions. In situations where conformity with the essential requirements must be based on clinical data [30]. The directive allows member states to "require the information, which must be made available to the user and the patient in their national language(s) or in another community language, when a device reaches the final user, regardless of whether it is for professional or other use". Consequently, the member states were required to specify in their implementing legislation the language to be used on any packaging and any labels. Naturally, although a number of options are provided, each country specified that their native language be mandatory [31].

Labeling Requirements in U.S.A.

The labeling of medical devices and in vitro diagnostic products are governed by two U.S. Federal laws [32]:

Fair Packaging and Labeling Act (FPLA)
Federal Food, Drug and Cosmetic (FFD&C) Act

Most of the provisions of the FPLA and the FFD & C Act are codified in the

following parts of Title 21 of the U.S. Code of Federal Regulations (CFR):

General Device Labeling	21 CFR Part 801
In Vitro Diagnostic Products	21 CFR Part 809
Investigational Device Exemptions	21 CFR Part 812
Good Manufacturing Practices	21 CFR Part 820
General Electronic Products	21 CFR Part 1010

The FFD & C Act is the primary law under which the FDA takes action against non-complying regulated devices, such as adulterated, misbranded (mislabeled) devices. Section 201 of the FFD & C Act defines the terms "label" and "labeling" as they apply to medical devices and draws a distinction between the two terms. Certain provisions apply specifically to the "label" of the device, others are related to its "labeling". Labeling is a very broad term and deals with labels on the device as well as descriptive and informational literature that accompany the device [33].

Table: 1 Type of Medical Devices (13)

Device License Type	Definition	Example
Single Device	A device that is identified with a unique name by its manufacturer and is sold as a distinct packaged entity.	Nebulizer
Medical Device Family	A group of medical devices that are made by the same manufacturer, that differ only in shape, colour, flavour or size, that have the same manufacturing process and that have the same intended use.	Urological catheters differing in size
Medical Device Group	A collection of medical devices, such as a procedure pack or tray that is sold under a single name.	Suture trays
Medical Device Group Family	A collection of medical device groups that are made by the same manufacturer, that have the same generic name specifying their intended use, and that only differ in the number and combination of the products that comprise each group.	Suture trays for differing applications
System	A medical device comprising a number of components or parts used together to fulfill all or some of the device's intended functions and which is sold under a single name. This includes an *In-vitro* diagnostic device (IVDD) system, but does not include processing devices that support numerous different assays and may be designated a system by the manufacturer.	Clinical chemistry system that has several assays of the same class with a dedicated analyzer
Test Kit	An in-vitro diagnostic device that consists of reagents or articles, or any combination of these, and that is intended to be used to conduct a specific test.	Hepatitis EIA kit

Use of symbols in medical device labeling

Symbols are often used on equipment in preference to words to save space and to preclude language differences, allowing easier comprehension. Care must be taken to ensure that the symbols are well understood and conform to the standards. When devising a global labeling strategy, particular emphasis should be placed on the following: evaluating the use of symbols to maximize label real estate; developing a consistent look and feel for labeling to maximize brand manifestation; planning for future languages to be added; and grouping languages together in a way that fits the company's distribution model (28).

The use of internationally recognized (i.e., standardized) symbols should be encouraged provided that device safety is not compromised by a lack of understanding on the part of the patient or user. Where the meaning of the symbol is not obvious to the device user (who, with some products, could be a member of the public), it should be described in words associated with the symbol [33]. This international standard identifies symbols conventionally used to convey information essential for proper use to the user and others for safe and effective use of medical devices. This international standard is primarily intended to be used by;

Manufacturers of medical devices, who market their products in a number of countries having different language requirements for medical device labelling;

Users of medical devices, who draw their supplies from a number of sources and may have varied language capabilities;

Those responsible for postmarket surveillance;

Health care regulatory authorities, testing organizations, certification bodies and other organizations responsible for implementing regulations affecting medical devices and having responsibility for postmarket surveillance [34]. The label of the inner and outer contained must contain the appropriate hazardous symbol and signal word. The symbol must be in printed in black on an orange-yellow background [35].

Multi-language Electronic Labeling for Medical Device Companies

A key practice that is assisting the process of writing the labels and translating them more effectively is the use of electronic labeling systems. Typically, there are text and symbols for each label which are used by several products in various media formats.

	Symbol for "Serial Number." This symbol shall be followed by, or above, the manufacturer's serial number.
	Symbol for "Batch Code." This symbol shall be adjacent to the manufacturer's batch code. The batch code may also be referred to as the lot number or batch number.
	Symbol for "Manufacturer." This symbol shall be adjacent to the name and address of the manufacturer.
	Symbol indicating the "date of manufacture." The symbol shall be adjacent to the date that the product was manufactured, expressed as four digits for the year and two digits for the month and where appropriate, two digits for the day.
	Symbol that may be used in place of the statement "CAUTION: U.S. Federal law restricts this device to sale by or on the order of a physician."
	Symbol for "Use By." This symbol shall be adjacent to the expiration date, as given in EN 28601, expressed as four digits for the year and two digits for the month and where appropriate, two digits for the day. This symbol is intended to indicate that the device should not be used after the end of the month shown, or the day, if applicable.
	Symbol for sterile medical devices processed using aseptic techniques.

	Symbol for method of sterilization using ethylene oxide.
	Symbol for method of sterilization using irradiation.
	Symbol for the method of sterilization using vaporized hydrogen peroxide.
	Symbol for method of sterilization using steam or dry heat.
NON-STERILE	Symbol indicating that the device has not been sterilized.
	Symbol for "do not re-use," "single use," or "use only once."
	Symbol for "Caution, consult accompanying documents" or "Attention, see instructions for use."
	Symbol for "Consult instructions for use" or "Consult operating instructions."

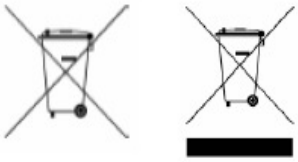
EC REP	Symbol for "Authorized Representative in the European Community." This symbol shall be adjacent to the name and address of the authorized representative in the European Community. The address is not required on an immediate container unless the immediate container is the outer container.
	Symbol for "temperature limitation." The upper and lower temperature limits will be indicated on either side of the symbol.
CE	This symbol is a mandatory marking for devices entering the European market to indicate conformity with the essential health and safety requirements set out in European Directives. The symbol may be accompanied by a four-digit identification number of the notified body. The vertical dimensions may not be less than 5 mm high.
	Symbol for "non-ionizing radiation." All equipment and systems that include RF transmitters or that intentionally apply RF electromagnetic energy for diagnosis or treatment must be labeled with this symbol.
	Symbol for "Shock protection type (B, BF, CF)."
	Symbol indicating "Not for general waste." For European Union (EU) States, this symbol should be used to mark devices that are reusable and not contaminated at the end of the device life.
	Symbol indicating to "Keep away from sunlight."
	Symbol used to indicate that the product should be kept dry.

Fig. 2: Symbols of medical device labeling and packaging

This practice removes the need to re-label and re-translate slightly modified products and allows re-use of content from previously produced labels. It modularizes content so that labels and other information can be assembled using a template. Second only to the U.S, the European medical device market represents an annual sales volume in excess of 40 Billion Euros and is increasing [36].

The nature of electronic labeling separates the text from the coding, typically in XML Extensible Markup Language type files. This makes layout and typesetting much simpler and cost effective for companies that previously had to assemble 17 language versions by hand. Electronic labeling allows companies to re-use text that is the same or similar for updates and product revisions. If navigating all these issues are not enough, you will also have to deal with placing multilingual text and symbols into the confined space of several labels. It is not until after this stage that translation is considered. If the information is not translated by a professional translator who understands the product and your industry, you may receive literal translations. For example, reverse-pipetting could be translated into German as use the pipette upside down [37].

Medical Device labeling for immediate container

The label of an immediate container should include the following information in a legible Manner [38, 39] Product name, Supplier name, Lot number, Expiration date, Contents, Identification of the device and intended use, In vitro use statement, Self-testing declaration, Caution statements, Storage information and Sterile device marking.

Medical Device labeling for immediate container small size medical devices

If the device is too small for a label that is large enough to fit the minimum required information, or if the label would interfere with the readability of the results, the information may be reduced to [40, 41] Product name,Supplier name,Lot number, Expiration date,Cautionary symbols (when applicable) and Indication of microbiological state.

Medical Device labeling For Outer container

The packaging that encloses the immediate container (s) to creating a single unit or an assembly of similar or dissimilar component, the label of the outer container should include the following information in a legible format [41], Product name,Supplier name , Lot number, Expiration date,Contents,

Identity of the device and intended use, In vitro use statement, Self-testing declaration, Caution statements, Storage information, Special operating instructions, Sterile device marking and Markings for investigational use

Misbranding Medical Device labeling

When labeling does not meet the FDA regulations in 21 CFR Part 801, the device is considered to be misbranded. The following activities would cause a device to be misbranded [42, 43]:

Its labeling is false or misleading in any particular, including promotion for unapproved uses.

It is in package form and its label fails to contain the name and place of business of the manufacturer, packer, or distributor; and an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.

Any required wording is not prominently displayed as compared with other wording on the device, or is not clearly stated.

Its label does not bear adequate directions for use including warnings against use in certain pathological conditions; or by children where its use may be dangerous to health; or against unsafe dosage, or methods, or duration of administration or application.

It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended or suggested in the labeling.

CONCLUSION

Complex and ever-changing international regulations controlling the marketing and usage of medical devices are forcing manufacturers to incorporate language translation and localization into global development strategies. A simultaneous global release of medical devices involving languages in globe makes this issue as critical as the intended purpose of the medical device. Medical device labeling should also include website addresses of manufactures, website must have full information of medical devices (how to use product, precaution during use and multilingual labeling) further these information must be in all the official languages of the world so that every person of the world would understand information. The harmonization of labeling requirements will be beneficial for pharmaceutical companies as well as patients because the labeling process becomes simpler, avoid unnecessary duplication of efforts, save time, reduced cost.

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